PATENT
Attorney Docket No. **AMGEN-08341**

#14 (4) Appeal Brief

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Marek Z. Kubin *et al.*
Serial No.: 09/667,859 Group No.: 1645
Filed: 09/20/2000 Examiner: B. Li
Entitled: **NK Cell Activation Inducing Ligand (NAIL) DNA And Polypeptides, And Uses Thereof**

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION - 37 CFR § 192)

Mail Stop Appeal Brief - Patents
Commissioner for Patents
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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

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Dated: September 22, 2003 By: Mary Ellen Waite
Mary Ellen Waite

Sir or Madam:

1. Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on **March 20, 2003**.

2. **STATUS OF APPLICANT**

This application is on behalf of

other than a small entity.

3. **FEE FOR FILING APPEAL BRIEF**

Pursuant to 37 CFR § 1.17(g), the fee for filing the Appeal Brief is:

Fee for Filing Appeal Brief $320.00

4. **EXTENSION OF TERM**

The proceedings herein are for a patent application and the provisions of 37 CFR § 1.136 apply.

Applicant petitions for a four month extension of time under 37 CFR § 1.136

(fees: 37 CFR §§ 1.17(a)-(d)).

Fee for Extension of Time $1450.00

5. **TOTAL FEE DUE**

The total fee due is:

Appeal brief fee $320.00

Extension fee (if any) $1450.00

TOTAL FEE DUE $1770.00

6. FEE PAYMENT

Attached is a check for **$1770.00**.

7. FEE DEFICIENCY

If any additional fee is required, charge Account No. **08-1290**.

Dated: September 22, 2003

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(1)

#14 (4) Appeal Brief 9.29.03

PATENT
Attorney Docket No. AMGEN-08341

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Marek Z. Kubin and Raymond G. Goodwin		
Serial No.:	09/667,859	Group No.:	1645
Filed:	09/20/2000	Examiner:	B. Li
Entitled:	**NK Cell Activation Inducing Ligand (NAIL) DNA and Polypeptides, and Uses Thereof**		

APPELLANTS' BRIEF

APPEAL NO.:

Mail Stop Appeal Brief - Patents
Commissioner for Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

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Dated: September 22, 2003

By: Mary Ellen Waite

Sir:

This Brief is in furtherance of the Notice of Appeal filed March 20, 2002.

The fees required under § 1.17(h) and any required Petition for Extension of Time for filing this Brief and fees therefore are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

This Brief is transmitted in triplicate. [37 C.F.R. § 1.192(a)].

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This Brief contains these items under the following headings and in the order set forth below [37 C.F.R. § 1.192(c)]:

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I. REAL PARTY IN INTEREST

The real party in interest is Immunex Corporation, now a wholly owned subsidiary of Amgen Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to Appellants, Appellants' legal representative, or the Assignee.

III. STATUS OF THE CLAIMS

Claims 1 - 47 were filed in the original application. During prosecution of the application, Claims 48 - 89 were added, and Claims 1 - 72 and 79 were cancelled. Claims 73 - 78 and 80 - 89 have been rejected by the Office in the Advisory Action dated May 19, 2003. Therefore, Claims 73 - 78 and 80 - 89 are pending in this appeal. No other claims are pending. Thus, Appellants appeal the Final Office Action of September 20, 2002 and the Advisory Action of May 19, 2003.

The Claims, as they now stand, are set forth in Appendix A.

IV. STATUS OF THE AMENDMENTS

Appellants' Amendment and Response to the Final Office Action filed on March 26, 2003 has been entered per the Advisory Action dated May 19 (2003)(Paper No. 12). Pursuant to this Amendment, the Office cancelled Claim 79 and maintained the rejections of Claims 73 - 78 and 80 - 89, as noted in Section III. Appellants have concurrently filed a revised Sequence Listing with this Appeal Brief per the Office's request in the Advisory Action.

V. SUMMARY OF THE INVENTION

The present invention relates to purified and isolated novel NAIL polypeptides, nucleic acids encoding such polypeptides, and processes for production of recombinant forms of such polypeptides, and the uses of the above. Sequences of these NAIL polypeptides and polynucleotides are provided in the Specification at p. 11, l. 7 - p. 13, l. 19; p. 14, l. 1 - p. 16, l. 35; p. 17, l. 19 - p. 20, l. 19; p. 25. l. 32 - p. 26, l. 5; p. 29, l. 19 - 28; and p. 33, l. 1 - 6 and in Figure 1. The NAIL polypeptides of the present invention and antibodies directed thereto have a number of uses, including, but not limited to, modulation of natural killer cell, cytotoxic T cell and B cell activity, selective enrichment of specific cell populations, induction of cytokine production and release, and detection and inhibition of MAIN binding to CD48. (Specification, p. 43, l. 26 - p. 50, l. 4; p. 71, l. 13 - p. 72, l. 18; p. 73, l. 27 - p. 74, l. 25; Figures 3, 4, and 7 for CD48 binding and stimulation of NK cells).

In particular, in some embodiments, the present invention is directed to isolated nucleic acid molecules that comprise a polynucleotide that encodes a polypeptide that is at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48. (Specification, p. 13, l. 11 - 18; Figures 3 and 4 for CD48 binding). In other embodiments, the present invention is directed to a nucleic acid molecule comprising a polynucleotide that is at least 80% identical to SEQ ID NO:1. (Specification, p. 11, l. 8 - 30). In still other embodiments, the invention is directed to nucleic acid molecules comprising a polynucleotide encoding a polypeptide comprising SEQ ID NO:6, SEQ ID NO:7, or SEQ ID NO:8. (Specification, p 25. l. 32 - p. 26, l. 5; p. 29, l. 19 - 28; and p. 33, l. 1 - 6). In further embodiments, the invention is directed to recombinant vector comprising the foregoing nucleic acid molecules and to host cells comprising such vectors. (Specification, p. 33, l. 15 - p. 39, l. 9; p. 67, l. 1 - 30). In still other

embodiments, the present invention is directed to methods of producing NAIL polypeptides wherein cells that are genetically engineered to express the foregoing nucleic acids are cultured under conditions that allow expression of the NAIL polypeptides. Id.

VI. ISSUES

There are four issues involved in the present appeal:

Issue 1 – Whether Claims 73 - 78 and 80 - 89 are enabled under 35 U.S.C. § 112, first paragraph.

Issue 2 - Whether Claims 73 - 78 and 80 - 89 are supported by an adequate written description under 35. U.S.C. § 112, first paragraph.

Issue 3 - Whether Claims 73 - 78 and 80 - 89 are patentable under 35 U.S.C. § 103(a) over Valiante et al. (U.S. Pat. No. 5,688,690), Sambrook et al. (Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43 - 2.84) and Porunellor et al. (J. Immunol. (1993) 151:5328 - 5337).

Issue 4 - Whether use of the term comprising renders the claims indefinite.

VII. GROUPING OF CLAIMS

Claims 73, 84, and 85 stand or fall together. The remainder of the Claims have separate and distinct limitations and must be considered independently.

Independent Claim 73 specifies an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

Dependent Claim 74 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide acid sequence is at least 90% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

Dependent Claim 75 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 22-221 of SEQ ID NO:2.

Dependent Claim 76 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 1-221 of SEQ ID NO:2.

Dependent Claim 77 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-221 of SEQ ID NO:2.

Dependent Claim 78 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-224 of SEQ ID NO:2.

Independent Claim 80 specifies an isolated nucleic acid molecule comprising a polynucleotide at least 80% identical to SEQ ID NO:1.

Dependent Claim 81 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:6.

Dependent Claim 82 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:7.

Dependent Claim 83 specifies the isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:8.

Multiple dependent Claim 84 specifies a recombinant vector comprising the nucleic acid molecule of any one of claims 73 through 83.

Dependent Claim 85 specifies a host cell transfected or transduced with the vector of claim 84.

Independent Claim 86 specifies a method for the production of NK cell Activation Ligand (NAIL) polypeptide comprising culturing a host cell that has been genetically engineered to express the nucleic acid of claim 73 under conditions promoting expression of the polypeptide.

Dependent Claim 87 specifies the method of claim 86, further comprising recovering the polypeptide.

Dependent Claim 88 specifies the method of claim 87, wherein the host cell is a mammalian cell.

Dependent Claim 89 specifies the method of claim 88, wherein the host cell is a CV-1/EBNA cell.

Claims 73, 84 and 85 have been grouped together. The remainder of the Claims could not be grouped when considered in light of each of the four issues presented above. The need for separate consideration of these Claims is underscored by the various deficiencies in the Office's rejections, which are described in more detail below in Section VIII. In particular, Appellant could not group these Claims because: 1) The Office's reliance on *Eli Lilly* to reject all of these Claims as lacking an adequate written description does not apply with equal force to these Claims because they are directed to particular sequences disclosed in the specification; and 2) The enablement rejection does not apply with equal force to these Claims because many of the claims are directed to the use of particular sequences.

VIII. ARGUMENT

A. Issue 1 - The Claims are Enabled

The Office rejected Claims 73 - 78 and 80 - 89 under 35 U.S.C. § 112, first paragraph as not being enabled by the specification. Although the Office conceded that the specification enables "an isolated nucleic acid molecule consisting of SEQ ID NO: 1 and its coding amino acid sequence SEQ ID NO: 2, wherein its functional fusion proteins are made by its amino acid residues 1-221 with tags (SEQ ID NOs: 6-8)," the Office asserted the specification does not reasonably provide enablement for having any or all polynucleotide or amino acids fragment thereof having 80% homology to SEQ ID NO: 1 or 2 to be a functional molecule like NAIL." (Paper No. 9 at pp. 2-3.)

The rejection is in error because the Office failed to establish a *prima facie* case of non-enablement. The standard to be applied in assessing enablement is whether the experimentation needed to practice the claimed invention is undue or unreasonable. *See* TRAINING MATERIALS FOR EXAMINING PATENT APPLICATIONS WITH RESPECT TO 35 U.S.C. SECTION 112, FIRST PARAGRAPH-ENABLEMENT CHEMICAL/BIOTECHNICAL APPLICATIONS, *citing In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). When applying this standard, the burden is on the Office to make a *prima facie* case of non-enablement that is well grounded in scientific reasoning or evidence. *See In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993); *See also* MPEP §706.03 and §2164.04. This is because without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling (*Wright,* 27 USPQ2d at 1513).

As described in detail below, Appellant respectfully submits that the Office failed to establish a *prima facie* case of non-enablement because: 1) The Office's arguments bear no

relation to the disclosure of the specification at issue; 2) Application of the *Wands* factors supports the conclusion that the claims are enabled; 3) The Office's arguments fail to consider the limitations of Claims 75 - 78 and 81 - 83; and 4) The Office has ultimately failed to present an argument that is well grounded in scientific reasoning or evidence.

1. The Office's arguments bear no relation to the disclosure of the specification at issue.

The Appellant has submitted extensive arguments (discussed in more detail in Section A.2.), supported by citation to the specification, as to why practice of the claimed invention would not require undue experimentation. However, instead of making arguments that are well grounded in scientific reasoning or evidence as to why undue experimentation is required in light of this specific disclosure, the Office made an inappropriate analogy to data for a completely different protein and reasoned that the claims are not enabled because of this unrelated data. In particular, the Office argued that the Applicant's argument is not persuasive because a "one amino acid mutation can turn out to be a functional different molecule." (Paper 9, p. 3). For support, the Office relied on the disclosure of Robin et al. and Stuffy et al. as evidence that unrelated human chemokines (e.g., MIP-2A, MIP-2B, GRO/MGSA, and RANTES) have different functions even though they are highly homologous.

This argument addresses neither the standard for enablement (undue experimentation) nor the evidence presented by Appellant. Importantly, the Office did not explain why this unrelated data is more persuasive on the issue of enablement than the actual teachings of the specification.

Instead, the Office stated that "Applicants do not present how to isolate any other polypeptide rather than SEQ ID NO: 6-8 having at least 80% homology to the SEQ ID NO:2 that exhibits the same function of NAIL." (Paper 9, p. 3). The Office is clearly mistaken given the teachings outlined below that precisely detail how to make and isolate such polypeptides.

2. Application of the *Wands* factors leads to the conclusion that the claims are enabled.

Appellant respectfully submits that proper analysis applying the *Wands* factors supports the conclusion that the claims are enabled. As described in the MPEP §2164.01(a), the Wands factors include: a) The breadth of the claims; b) The nature of the invention; c) The state of the prior art; d) The level of ordinary skill in the art; e) The level of predictability in the art; f) The amount of direction provided by the inventor; g) The existence of working examples; and h) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See also, In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). As noted in the MPEP:

> It is improper to conclude that a **disclosure is not enabling** based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all of the evidence related to each of these factors, and any conclusion of non-enablement must be based on the evidence as a whole.

MPEP §2164.01(a)(citing *In re Wands*, 858 F.2d 731, 740 (Fed. Cir. 1988)(emphasis added)).

Appellant respectfully submits that the Office's analysis, discussed in more detail below, completely fails to address **any** of the *Wands* factors. As noted in the MPEP, the analysis must be of the **disclosure**.

During prosecution of the instant Application, Appellant has cited extensively to the **disclosure** of the specification for support that the claims are enabled. As Appellant has argued, because the cDNA (SEQ ID NO:1) and amino acid sequences (SEQ ID NO:2) are provided in

the specification, it is straightforward to determine what variations of these nucleotide and amino acid sequences falls within the 80% sequence identity limitation recited in the claims while maintaining the property of binding CD48. Such variations are described in the specification on pages 18-20 and 24-27, and include those differing from native SEQ ID NO:1 due to mutations, restriction digests, ligation to addition sequences, and chemical synthesis, for example; and those differing from SEQ ID NO:2 due to deletions, insertions, substitutions, and fusions, for example. These additional molecules can be generated according to methods described in the specification and methods well known in the art, such as those provided on pages 18-20, 24-27, 25-33, and Example 3, page 67. A computer program for comparing sequence identity is provided on pages 19 (for nucleotide) and 24 (for amino acid) of the specification. Binding of the polypeptide to CD48 can be determined, for example, using the assays described in detail on pages 46 and 47, and equilibrium binding assays described in Example 8, page 71. In addition, the specification describes on pages 21-24 how to generate fragments of SEQ ID NO:2, and how to test for the ability of the fragment to bind to CD48.

This evidence establishes that the specification teaches in detail how to: 1) make variants of SEQ ID NOs: 1 and 2; 2) calculate the percent identity between SEQ ID NOs: 1 and 2 and the variant sequence; and 3) test the variant sequence to determine if it binds to CD48.

Application of the *Wands* factors to these facts supports the conclusion that the claims are enabled. First, the present invention is in the field of molecular biology. The *Wands* court has already held that the level of skill in this art is high. *Wands*, 858 F.2d at 740. Second, as the extensive citations to the specification above prove, the specification provides considerable guidance and direction for producing the claimed nucleic acid sequences. Third, as in *Wands*, the methods of making the claimed nucleic acid sequences and screening for activity are known

in the art and described in the specification at the cited passages. *Id.* Fourth, as admitted by the Office in Paper No. 9 at pp. 2-3, the specification provides working examples of several sequences within the scope of the claims (i.e., SEQ ID NOs: 1, 2, and 6-8). Fifth, given the extensive guidance given in the specification (cited above) and the high level of skill in the art, the experimentation involved to produce other sequences within the scope of the claims is well within the skill of those in the art. As held by the *Wands* court: "The test is not merely quantitative since as considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed. *Id.* at 737.

Turning to the claims at issue, as part of the enablement analysis, the scope of the claims must be considered. MPEP § 2164.04. Independent Claim 73 is directed to an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48. Dependent Claim 74 further specifies the polypeptide encoded by the claimed polynucleotide must be 90% identical to amino acids 22-221 of SEQ ID NO:2. Independent Claim 80 is directed to an isolated nucleic acid molecule comprising a polynucleotide at least 80% identical to SEQ ID NO:1.

As described above, given the high level of skill in the art, extensive guidance in the specification, methods known in the art, the production of and isolation of the claimed nucleic acid sequences which are greater than 80% identical to SEQ ID NO:1 or which encode polypeptides that are more than 80% identical to SEQ ID NO:2 and which bind CD48 do not require undue experimentation. Thus, Appellant respectfully submits that Claims 73, 74 and 80 are enabled. Claims 84 - 89 are directed to host cells, vectors, and methods utilizing the sequences of Claim 73 and thus the same reasoning that applies to enablement of Claim 73

applies to these Claims. Appellant notes that the Office has not addressed these Claims separately thus believe that the additional elements of these Claims do not raise additional enablement issues.

3. The Office's arguments fail to consider the limitations of Claims 75 - 78 and 81 - 83

The facts and analysis above provide even stronger support for concluding that the remaining claims are enabled. Claim 75 - 78 and 81 - 83 are directed to specific sequences and do not contain the homology element that the Office objected to. Appellant notes that the Office did not addressed these Claims separately thus believe that the additional elements of these Claims do not raise additional enablement issues. Thus, Appellant respectfully submits that these Claims are enabled.

4. The Office has ultimately failed to present an argument that is well grounded in scientific reasoning or evidence.

The burden is on the Office to make a *prima facie* case of non-enablement that is well grounded in scientific reasoning or evidence. *See In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993); *See also* MPEP §706.03 and §2164.04. Appellant respectfully submits that the Office did not make properly reasoned and scientifically supported statements explaining Applicant's alleged failure to comply with 35 U.S.C. §112. As described above, analysis of the teachings of the specification according to the *Wands* factors support a conclusion that practice of the claims does not require undue experimentation. However, instead of considering the language of the claims and the teachings of the specification in light of the *Wands* factors, the Office resorted to

the use of evidence that bears no relation to the claimed nucleic acids, vectors, cell lines and methods. Thus, the Office failed to provide **any** scientific reasoning or evidence that is specific to the claims at issue. Thus, Appellant respectfully submits that the Office did not make a *prima facie* case of enablement. Accordingly, Appellant respectfully requests that this ground of rejection be removed.

B. Issue 2 - The Claims are Supported by an Adequate Written Description

The Office rejected Claims 73 - 78 and 80 - 89 under 35 U.S.C. § 112, first paragraph as not being supported by an adequate written description. In particular, the Office asserted that the described invention is limited to SEQ ID NOs:1, 2, 6, 7 and 8, shown to have the biological properties of encoding NAIL (specifically, the ability to bind CD48), and that the specification does not provide a written description of any additional sequences. Appellant respectfully submits that this rejection is in error.

In maintaining the rejection, the Office relied upon *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir, 1997), stating that the instant "situation would be the same to the Eli Lilly Co. because some sequence generated from a host, rather than human, may accidentally have 80% homology to the SEQ ID NO: 1 or 2." (Paper No. 9, p. 4). Appellant submits that this statement is both unsupported by the evidence of record, and immaterial to whether the standards for written description have been met for the instantly claimed invention. Further, the Office did not address Appellant's point in the previous reply that the rejection is inconsistent with the USPTO's own guidelines for examination under the written description requirement. The Office may not simply ignore this argument. Recent Federal Circuit precedent establishes that determinations of whether the written description requirement have been met

should be consistent with both Federal Circuit precedent and the written description guidelines. *Enzo Biochem, Inc. v. Gen-Probe, Incorporated*, 323 F.3d 956 (Fed. Cir. 2002).

Contrary to the Office's assertions and in sharp contrast to the situation in *Lilly*, the specification does indeed show that the Inventors had possession of the claimed invention. Specifically, the Inventors cloned the human cDNA that encodes NAIL, identified the NAIL binding partner as CD48, and described not only the nucleic acid molecules noted by the Office, but also contemplated and described a wide variety of variants of these molecules (*e.g.*, mutations, conserved changes, deletions, fusions to sequences encoding useful domains such as Fc's, etc.) at pages 17-33. Thus, it is clear that the Inventor's contemplated and were in possession of the claimed invention.

In addition, the Office provided no explanation as to why its interpretation of *Lilly* is inapposite to the guidelines promulgated by the USPTO. Appellant again refers the Office to the USPTO's "Synopsis of Application of Written Description Guidelines" (pertinent pages attached at Appendix B). Appellant previously referred the Office to Example 14, pages 53-55. The claim of Example 14 recites a protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A->B. The disclosure of Example 14 provides a single species (SEQ ID NO:3) that has actually been reduced to practice, and describes an assay for identifying the variants having the desired catalytic activity. The analysis considers (1) whether the members of genus vary substantially from each other; and (2) whether the disclosed species is representative of the members of the genus; in order to determine whether one of skill in the art would determine if the applicant was in possession of the necessary common attributes possessed by the members of the genus.

For Example 14, it was determined that the member species did not substantially vary since the variants have 95% identity or greater to the reference sequence, and also possess the catalytic activity. It was also determined that the disclosed species was representative since all members must have at least 95% structural identity to SEQ ID NO:3. The analysis determined that one of skill in the art would conclude that the applicant was in possession of the necessary common attributes possessed by the members of the genus, and therefore the disclosure in this Example meets the written description requirement. Appellant submits that the polypeptides encoded by the polynucleotides of claims 73, 74 and 80 can be analyzed in a similar manner to that provided in Example 14. First, the polypeptides encoded by the polynucleotides do not substantially vary as members of a genus since they all have at least 80% (or 90%) identity to SEQ ID NO:2 and possess the same binding activity. Second, the polypeptide having SEQ ID NO:2 is a representative species of the genus since all polypeptides must have at least 80% (or 90%) identity to this sequence. Therefore, one of skill in the art would conclude that the Inventors were in possession of the necessary common attributes possessed by the members of the genus, and therefore the instant specification meets the written description requirement for these claims.

Claims 84 - 89 are directed to host cells, vectors, and methods utilizing the sequences of Claim 73 and thus the same reasoning that applies to Claim 73 applies to these Claims. Appellant notes that the Office did not address these Claims separately thus believe that the additional elements of these Claims do not raise additional written description issues.

Finally, the Office's arguments are even less applicable to the remaining claims. Claim 75 - 78 and 81 - 83 are directed to specific sequences and do not contain the homology element that the Office focused on for the rejection. Thus, the Office's *Eli Lilly* based arguments **do not**

apply to these Claims. Appellant notes that the Office did not address these Claims separately and believe that the additional elements contained in these Claims overcome the Office's rejections.

In light of the statements set forth above, Appellant respectfully requests that the Office reconsider and withdraw the rejections of the claims on the basis of the 35 U.S.C. § 112, first paragraph, written description requirement.

C. Issue 3 - The Claims Are Not Obvious

Claims 73 - 78 and 80 - 89 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Valiante et al. (U.S. Pat. No. 5,688,690), Sambrook et al. (Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor, N.Y. 1989, pp. 2.43 - 2.84) and Porunellor et al. (J. Immunol. (1993) 151:5328 - 5337). Appellant respectfully submits that this rejection is in error because the Office failed to establish a *prima facie* case of obviousness with respect to any of the pending Claims.

A *prima facie* case of obviousness requires the Office to cite a reference, or combination of references, that (a) disclose all of the elements of the claimed invention, (b) provide a suggestion or motivation to one of skill in the art to combine the elements to yield the claimed combination, and (c) provide a reasonable expectation of successfully carrying out the claimed combination. See M.P.E.P. § 2143; see also *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). Failure to establish any one of the three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles the Appellant to allowance of the claims at issue. In this case, the Office failed to establish that the cited references teach element of the claims and that the combination of the references is proper.

1. The Cited References Do Not Teach Each Element of the Claims

The cited references, alone or in combination, fail to teach a single nucleic acid molecule encoding a polypeptide at least 80% or 90% identical to SEQ ID NO: 2 as required by Claims 73, 74, and 84 - 89, much less the specific nucleic acid sequences specified in the remainder of the claims. In fact, the Office provided **no** evidence establishing that any of the three references disclose any nucleic acid molecule even remotely related to the claimed sequences.

Appellant respectfully submits that the primary mistake made by the Office is highlighted in the Advisory Action where the Office stated that "it is the Applicants burden to approve [sic] that the claimed **polypeptide** and the p38 disclosed by Valainte et al. are isolated from the same source (human NK cells stimulated with IL2, IL12), have the same molecular weight (p38 Kd) and are recognized by the same monoclonal antibody (CI.7)." (Paper No. 12, p. 5, emphasis added). Appellant must emphasize that the present claims are to **nucleic acid sequences, not polypeptides**.

This distinction is dispositive. As previously argued, the facts in the instant application are similar to the case of *In re Deuel,* 34 USPQ2d 1210 (Fed. Cir. 1995), in which claims reciting isolated DNA and cDNA molecules encoding heparin-binding growth factors were rejected as obvious over two references. The first reference to Bohlen described heparin-binding brain mitogens in terms of molecular weight and 19 N-terminal amino acid sequences, and the second reference, Maniatis et al., was a general reference describing methods of molecular cloning. The obviousness rejection in *Deuel* was based on the Office's assertion that it would have been *prima*

facie obvious to one of ordinary skill in the art at the time of the invention to use the methods of Maniatis et al. and the 19 N-terminal amino acids of Bohlen to clone the genes encoding the heparin-binding growth factors. This rejection was overturned *en banc* by the Federal Circuit, stating that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious..." (at 1215). "Because Deuel claims new chemical entities in structural terms, a *prima facie* case of unpatentability requires that the teachings of the prior art suggest the claimed compounds to a person of ordinary skill in the art." A *prima facie* case of obviousness in this situation, the court continued, must be based on structural similarity to a prior art compound, such as homologs (see page 1214).

As in *Deuel*, the Office has failed to provide a reference showing or suggesting a structurally similar composition to compare with the recited compositions of matter in the instant claims. As in *Deuel*, it is not proper for the Office to use the p38 protein identified in the '690 patent together with the methods such as those described in Sambrook et al. to reject claims drawn to specific sequences. In fact, the p38 molecule of the '690 patent is described in even less detail than that of the Bohlen reference cited against the claims in *Deuel,* which provided the 19 N-terminal amino acid sequences.

The Office's reliance on Porunellor does nothing to cure the deficiencies in the Office's reasoning. As described in the instant specification (pages 13-16), the nucleotide sequences encoding mouse 2B4 and human NAIL polypeptides, and the amino acid sequences of mouse 2B4 and human NAIL have been compared. The nucleotide sequences are 69% identical and the amino acid sequences are 54% identical (page 13 of the specification). An inspection of the amino acid sequence alignment between HuNAIL amino acids (amino acids 22-221, 1-221, 19-

224) and 2B4 amino acids in that section of the sequence indicates less than 80% identity, and thus the 2B4 sequence does not fall within the limits of the claims. In addition, the nucleotide sequences of mu2B4 and huNAIL have only a 69% identity, and therefore do not fall within the 80% identity limit recited in claim 80.

Accordingly, the Office failed to present any evidence that the cited references teach the 80% identity limitation of Claims 73, 80 and 84 - 89, the 90% identity limitation of Claim 74, or the specific sequences Claims 75 - 78 and 81 - 83. Accordingly, the Office failed to establish a *prima facie* case of obviousness and the Claims should be passed to allowance.

2. The Office Has Shown No Evidence of a Motivation to Combine the References

The Office's entire rejection rests on a factually unsupported (and unsupportable) conclusory statement. As the Federal Circuit has stated, "[b]efore the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *In re Jones,* 958 F.2d 347, 351 (Fed. Cir. 1992) (*citing In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988)); *see also* M.P.E.P. § 2143.01. In making the obviousness rejection, the Office merely stated what the references purportedly teach and then states "it would have been obvious to one of ordinary skill in the art at the time of [sic] the invention was filled [sic] to be motivated by the recited reference Valiante et al. and combine the methods taught by et Valiante et al. Sambrook et al. and Porunellor et al. to either use the monoclonal antibody or cDNA to isolate the protein corresponding to the protein having the function of activating NK cell through binding the

molecule of CD48." (Paper No. 9, p. 7). This statement is conclusory because it merely recites the references and says that they can be combined to produce the claimed results. The Federal Circuit has expressly forbidden this hindsight-based approach.

Specifically, the Federal Circuit held that:

> The factual inquiry whether to combine references must be thorough and searching. It must be based on **objective evidence** of record. **This precedent has been reinforced in myriad decisions, and cannot be dispensed with.**

See, In re Lee, 277 F.3d 1338, 1344 (Fed. Cir. 2002); internal citations omitted; emphasis added. Indeed, the Federal Circuit has made it clear that "[b]road, **conclusory** statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999)(emphasis added).

Thus, the Office's conclusory motivation statement falls well short of the standards established by the Federal Circuit. In particular, the Office provided no rationale as to why a person of ordinary skill in the art would be motivated to combine Valiante et al. and Porunellor et al. when there is absolutely no evidence in either of those references indicating that the disclosed molecules have any relation to one another. Given this fact, it is apparent that the Office applied hindsight reconstruction to reject the claims. This is the situation that the above standards are meant to prevent:

> The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. **Instead, the Board merely invoked the high level of skill in the art.** If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness (Emphasis added).

In re Rouffet, 47 USPQ2d 1453 (Fed. Cir. 1998). Accordingly, Appellant respectfully submits that the Office failed to establish a *prima facie* case of obviousness because the Federal Circuit standards for motivation to combine have not been met. As such, the obviousness rejection should be removed.

D. Issue 4 - The Claims are Definite

In the Final Office Action (Paper No. 9) the Office rejected Claims 73 - 84 under 35 U.S.C. § 112, second paragraph as indefinite due to use of the term comprising. Appellant respectfully notes that the Advisory Action (Paper No. 12) does not address the Appellant's arguments regarding this rejection. Accordingly, Appellant believes that this ground of rejection has been removed.

In the event this rejection is still pending, Appellant respectfully submits that it is in error for the following reasons. The Office asserted that the open language of "comprising" fails to define the precise structure of the claimed nucleic acid sequences and the elements that are not taught or cannot be defined or described from the specification. (Paper No. 9 at p. 2.) Appellant believes that by this rejection is meant that the structure of the claimed isolated nucleic acid molecules is thought indefinite because transitional term "comprising" is open, and hence the isolated nucleic acid molecules may have additional sequences or elements (such as, for example, sequences encoding promoters, polyadenylation signals, replication origins, selectable markers, etc.). The Office requested that the claim be amended to claim "a precise sequence structure of the intended molecule(s)." By this statement, Appellant understood that if the claims were rewritten in closed language to claim an isolated nucleic acid molecule containing only the recited sequence, the rejection would not apply. This request by the Office is in error.

In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the Office must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope and, therefore, serves the notice function required by 35 U.S.C. § 112, second paragraph. *See* MPEP § 2173.02. Appellant submits that the proper standard for definiteness under § 112 (as established in case law, and as enunciated in the Patent Office's guidelines, examining practices and procedures) has not been followed in applying this rejection.

The only reason given for rejecting the pending claims as indefinite is the use of the transitional term "comprising." There has been no assertion that the recited claim limitations are indefinite or that the public would not know whether a composition having the recited element falls within the scope of the claim. Instead, the Office asserted the claims are indefinite because other elements can form a structure with the recited element. But, if one of skill can tell whether the recited limitations are within the structure, the reason advanced by the Office is not an allowable basis for an indefiniteness rejection.

Furthermore, the term "comprising" is well established and understood, and does not in itself render claims indefinite. "Comprising," when used in claim language, means "the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech , Inc. v. Chiron Corp.*, 42 USPQ2d 1608 (Fed. Cir. 1997). "For example, a pencil structurally infringing a patent claim would not become noninfringing when incorporated into a complex machine that limits or controls what the pencil can write. Neither would infringement be negated simply because the patentee failed to contemplate use of the pencil in that environment." *A.B. Dick Co. v. Burroughs Corp.*, 218 USPQ 965 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1042 (1984).

The Office also asserted that additional elements are not taught or not described in the specification. Appellant submits that there is no authority under 35 U.S.C. § 112, second paragraph, which requires applicants for a patent to describe other unclaimed elements that, in combination with the recited elements, can form a structure within the scope of claims drafted in open format. Moreover, Appellant notes for the record that they have described a great variety of different "elements" that can be used in combination with the recited sequences. Appellant draws the Office's attention to pages 33-39 of the instant specification which describes, among other things, expression plasmids, hosts, etc. In addition, the Inventors have provided actual working examples of isolated nucleic acid molecules containing additional "elements." For example, on page 65 of the specification, the Inventors describe isolation of the clone Hup38, which comprises a NAIL cDNA cloned into the mammalian expression vector pDC409. As another example, on page 67, additional constructs made were: (1) a FLAG, poly-His tagged soluble form of NAIL encoded by DNA contained within the expression vector pDC412; and (2) a leucine zipper, poly-His tagged soluble form of NAIL encoded by DNA contained within the expression vector pDC412.

In summary, the Office's request that Appellant amend its claims to recite closed language is not supported by the law under 35 U.S.C. § 112, second paragraph and, if followed, would vitiate the reasons for pursuing patent protection on Appellant's claimed invention.

In view of the above, Appellant requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

E. Conclusion

For the foregoing reasons, it is submitted that the Office's rejection of Claims 73 - 78 and 80 - 89 was erroneous, and reversal of the rejection is respectfully requested. Appellant requests either that the Board render a decision as to the allowability of the claims, or alternatively, that the application be remanded for reconsideration by the Office.

Dated: 9-22-03

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APPENDIX A

PENDING CLAIMS

The following is a list of the pending Claims.

73. An isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

74. An isolated nucleic acid molecule of claim 73, wherein the polypeptide acid sequence is at least 90% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48.

75. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 22-221 of SEQ. ID NO:2.

76. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 1-221 of SEQ ID NO:2.

77. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-221 of SEQ ID NO:2.

78. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises amino acids 19-224 of SEQ ID NO:2.

80. An isolated nucleic acid molecule comprising a polynucleotide at least 80% identical to SEQ ID NO:1.

81. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:6.

82. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:7.

83. The isolated nucleic acid molecule of claim 73, wherein the polypeptide comprises SEQ ID NO:8.

84. A recombinant vector comprising the nucleic acid molecule of any one of claims 73 through 83.

85. A host cell transfected or transduced with the vector of claim 84.

86. A method for the production of NK cell Activation Ligand (NAIL) polypeptide comprising culturing a host cell that has been genetically engineered to express the nucleic acid of claim 73 under conditions promoting expression of the polypeptide.

87. The method of claim 86, further comprising recovering the polypeptide.

88. The method of claim 87, wherein the host cell is a mammalian cell.

89. The method of claim 88, wherein the host cell is a CV-1/EBNA cell.